IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Epperson, Jon D.
JIM WELLS, et al.	)	Art Unit: 1639
Application Serial No. 09/981,547	)	Confirmation No: 8070
Filed: October 17, 2001	)	Attorney's Docket No. 39750-0002D1
For: METHODS FOR RAPIDLY IDENTIFYING SMALL ORGANIC MOLECULE LIGANDS FOR BINDING TO BIOLOGICAL TARGET MOLECULES	)	**Customer No. 25213**

EXPRESS MAIL LABEL NO.: EV 582 624 410 US
DATE MAILED: JUNE 21, 2006

ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANTS' REPLY BRIEF TO EXAMINER'S ANSWER

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents -
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

This is a Reply Brief in response to the Examiner's Answer mailed on April 27, 2006 to the Appeal Brief filed on December 2, 2005 appealing the rejection of claims 58, 59, 61, 65, 81-89, 93, 95 and 96 in the Office Action mailed on May 25, 2005. This Reply Brief is accompanied by a Request for Oral Hearing.

ARGUMENTS

According to the Examiner's Answer, all claims under examination (claims 58, 59, 61, 65, 81-89, 93, 85 and 96) remain rejected under 35 U.S.C. 103(a) over Kim et al. (WO 98/11436) and Siuzdak (G. Mass Spectrometry for Biotechnology, New York: Academic Press, 1996, pages 119-126) and Kindal et al. (WO 97/01755).

APPELLANTS' REPLY TO THE EXAMINER'S ANSWER

A detailed rebuttal of the outstanding rejections was provided in the Appeal Brief filed on January 28, 2004. Instead of rearguing the case, in the present Reply Brief, Appellants wish to focus on the major deficiencies in the Examiner's position, as set forth in the Examiner's Answer. Appellants specifically maintain all prior arguments, submitted in response to the prior rejections and in their Appeal Brief.

The Invention and the Rejections

The invention claimed in the present application is a method for identifying a non-oligomeric organic compounds that has the greatest relative affinity for the target protein from a library of non-oligomeric organic compounds, less than 2000 daltons in size, that are capable of binding covalently to a chemically reactive group on the target protein to form a target protein-ligand conjugate. The target protein and the library are contacted with each other in a mixture, and once a target protein-compound conjugate is formed, the mixture is analyzed by mass spectrometry. Using mass spectrometry, (1) the target protein-compound conjugate is detected, (2) the identity of the non-oligomeric organic compound present in the conjugate is determined, and (3) the compound is identified as having the greatest relative affinity for the target protein from the compounds present in the library analyzed. Thus, the method results in the identification of a novel ligand for the target protein.

A similar method is disclosed in Kim *et al.* with the significant difference that the only method specifically disclosed in Kim *et al.* for the detection of ligands that bind to a target protein is detection using antibodies (page 21, second sentence of first full paragraph). As the

Examiner has acknowledged, Kim *et al.* does not teach the use of mass spectrometry. As to this point it is important to note that in the present invention mass spectrometry is used not only to detect a ligand bound to the target protein, but also to determine the identity of the so far unknown ligand bound, and to as identify the ligand (the identity has now been determined) as having the greatest relative affinity for the target protein from the compounds present in the library analyzed. Thus, the missing disclosure from Kim *et al.* is not simply the teaching of mass spectrometry as a detection technique, but the teaching of mass spectrometry as a technique for detecting and identifying a particular ligand from among an often large number of ligand candidates. The Examiner relies on Siuzdak and Jindal *et al.* as allegedly supplying this missing teaching.

The Examiner's Answer

The Examiner holds that "[i]t would have been obvious to one skilled in the art at the time the invention was made to 'identify' target/ligand interactions using the 'affinity enhancing' techniques as taught by Kim *et al.* with mass spectroscopy as taught by the combined references of Siuzdak and Jindal *et al.* because Jindal *et al.*, for example, explicitly state that mass spectrometry can be applied to the study of target/ligand interactions including the use of combinatorial libraries . . . , which would encompass the libraries disclosed by Kim *et al.* (i.e., the references represent analogous art)." (Examiner's Answer, page 9, lines 5-12.) The Examiner further argues that a person skilled in the art would have been motivated to use mass spectroscopy "as disclosed by the combined references of Siuzdak and Jindal *et al.* because Jindal *et al.*, for example, state that their technique improves upon the prior art by increasing the speed by which the target/ligand interactions can be screened, facilitating the use of automation, increasing the sensitivity of the method, and provides enough information about the ligand to facilitate its molecular 'identification' thus preventing the need for further characterization by some analytical technique." (Examiner's Answer, page 9, lines 12-18.) The Examiner additionally argues that "Siuzdak explicitly shows that the technique [electrospray mass spectrometry] can be applied to both 'covalent' and 'non-covalent' including antibody/antigen interactions." (Page 10,lines 17-18 of the Examiner's Answer.) The Examiner finds the latter

particularly important in his attempt to show motivation for combining the cited reference, emphasizing that Siuzdak *et al.* discloses that "BOTH 'covalent' and 'non-covalent' interactions can be measured (and distinguished) using mass spectrometer." (Page 11, lines 10-11, emphasis original.)

In addressing Appellants' arguments concerning the dismissal of the Siuzdak Declaration, which contradicted the Examiner's reading of this citation, the Examiner asserts that the "Siuzdak Declaration does not fully address the current rejection. The Siuzdak Declaration was submitted on 2/28/05, which predates the 5/25/05 Jindal *et al.* rejection and, as a result, it is not applicable to the current rejection." (Examiner's Answer page 13, lines 9-11, emphasis added.) The Examiner further states that the Siuzdak Declaration is not commensurate in scope with the claims since the claims do not require the use of mass spectrometry for the "identification" of covalently bound protein-ligand conjugates in a mixture as purported. (Examiner's Answer, passage bridging pages 13 and 14.) The Examiner further notes that the claims do not require the use of an "unknown" library (page 14, first full paragraph and page 20, line 7 of the Examiner's Answer), and notes that "Appellants [sic] arguments fail to set forth any plausible reason why a 'known' compound (i.e., a known structure) couldn't be analyzed with a mass spectrometer." (Examiner's Answer, page 20, lines 13-14.) The Examiner adds that that even if all of this was not true, the "comprising" language of the claim would allow the use of other techniques before introduction of a mass spectrometer. (Examiner's Answer, passage bridging pages 14 and 15 and page 21, lines 1-4.) Finally, the Examiner notes that the Siuzdak Declaration is merely conclusory without providing any factual information, and notes, with sarcasm, that "[i]f library mixtures were really hard to characterize as purported by Dr. Siuzdak then the Declarent [sic] should have had no trouble documenting this assertion with supporting evidence (e.g. a paper showing that it was hard to analyze a library.)." (Examiner's Answer, page 15, lines 10-13 and page 21, lines 13-16.)

Appellants' Reply

(1) The Examiner's comments on the claim language and listing of various theoretical possibilities of reading the claims in a way that supports the current rejections are improper. It is well established that the claims are to be interpreted in view of the specification. See, In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The prosecution history may assist in defining claim terms, and may limit the interpretation of a claim term so as to exclude any interpretation that would encompass subject matter disclaimed during prosecution. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582-83 (Fed. Cir. 1996) (citing Southwall Tech., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1576 (Fed. Cir. 1995)). It is also well established that "[w]here there is an equal choice between a broader and a narrower meaning of a claim, and there is an enabling disclosure that indicates that the applicant is at least entitled to a claim having the narrower meaning," the court should "adopt[] the narrower meaning." Athletic Alternatives, Inc. v. Prince Mfg., Inc., 773 F.3d 1573, 1581 (Fed. Cir. 1996). The same principle should be applied when reading the claims at issue in the present application. Both the specification and the prosecution history make it clear that in the method claimed in the present application mass spectrometry is used to both detect a ligand bound and to determine its identity. Therefore, any other reading of the claims is forced, and serves only to find a better foundation for the otherwise unfounded rejections.

(2) It is erroneous to say that, since the Siuzdak Declaration was filed before the citation of Jindal *et al.* and thus "does not fully address the current rejection," it is "not applicable to the current rejection." There is no legal requirement about what a Declaration should or should not address, and there is certainly no legal requirement that a Declaration should "fully address" a rejection. Expert Declarations are filed to make or substantiate a certain point or argument, and should be viewed along with other arguments and evidence of record. The Siuzdak Declaration clearly meets this standard, and is powerful evidence of record for the purpose for which it has been submitted.

The relevant problem solved by the present invention is: (1) the detection, in a mixture of target protein-compound conjugates, the most abundant conjugate, and the determination of the identity of the compound present in the conjugate, which will be the compound having the greatest relative affinity for the target protein of the compounds present in the mixture assayed (Claim 58); or (2) the detection of the most abundant protein-compound conjugate formed in a mixture containing the target protein, at least two compounds that are capable of forming a conjugate with the target protein through disulfide bond formation, and a reducing agent (Claim 86). The Siuzdak Declaration clearly establishes that mass spectrometry would not have been a method of choice for either case.

As Dr. Siuzdak explains in paragraph 6 of his Declaration *"[w]hile electrospray ionization mass spectrometry is well suited to study enzymatic mechanisms where all of the participants are known, its use to analyze mixtures of unknown components is limited."* One reason for this is that *"heterogeneous compounds can produce complicated spectra that can be difficult or impossible to interpret."* Another obstacle is that *"heterogeneous mixtures tend to reduce the sensitivity of electrospray ionization mass spectrometry."* Dr. Siuzdak adds that *"these obstacles are shared by other technique of mass spectrometry."* In view of this explanation, in paragraph 7 Dr. Siuzdak states: *"I do not believe that a person skilled in the art would have assumed that mass spectrometry techniques to study enzymatic mechanisms would have been applicable to identify novel ligands by the mass spectrometry analysis of a mixture of unknown chemical entities, detecting a covalently bound protein-ligand conjugate from among the chemical entities present in the mixture, and determining the identity of the ligand present in the conjugate detected."* The citation of Jindal *et al.*, as discussed below, does not change this conclusion.

Furthermore, the Examiner's remark that "[i]f library mixtures were really hard to characterize as purported by Dr. Siuzdak then the Declarent [sic] should have had no trouble documenting this assertion with supporting evidence (e.g., a paper showing that it was hard to analyze a library.)," is unwarranted, since it questions the credibility of the Declarant, without any foundation. Dr. Siuzdak is a person unquestionably skilled in the art, who has based the

opinions expressed in his Declaration on his many years of distinguished career in the field of mass spectroscopy, and his personal experience. Furthermore, his Declaration served to eliminate certain misconceptions about the reading and interpretation of his own work, as it was applied by the Examiner in the pending rejections. There is no reason to interpret Dr. Siuzdak's failure to cite any additional paper showing that it was hard to analyze a library as a deficiency, or as a ground to question the Declarant's credibility. Furthermore, as the Examiner is fully aware, negative results are typically not published, therefore finding a paper reporting a negative result is by far not as simple as the Examiner makes it out to be.

(3) As stated about, Jindal *et al.* does not contradict the conclusions of the Siuzdak Declaration. Jindal *et al.* disclose a complex chromatography-based screening method for identifying a ligand for a target of interest in a peptide library. The mixture screened contained three types of peptides: those that (i) have no affinity to any protein; (ii) bind to a large number of proteins; and (iii) show affinity to a specific target protein. The screening system of Jindal *et al.* differentiates among these various peptides using a series of chromatographic steps, each based on a different physico-chemical characteristic, ultimately leading to the separation of one or more ligands for the target protein, which are then identified by any method known in the art suitable for detection, including mass spectrometry and subsequent peptide sequencing. This is in contrast with to the present invention, which does not involve such separation steps, and where a complex mixture of target protein-ligand conjugates and optionally ligand candidates is analyzed by mass spectrometry, allowing the determination of the identity of a particular ligand from among the conjugates and ligand candidates present, which typically tend to have very similar molecular weights.

The selective citations from Jindal *et al.*, which were picked and chosen from unrelated part of the disclosure, omitting important parts and inserting the Examiner's own interpretations and thoughts without any support or foundation in the reference itself have been extensively discussed in the Appeal Brief. In order to avoid lengthy repetitions, Appellants only wish to address one particular citation that the Examiner used in support of the notion that "mass spectroscopy is the method of choice for studying libraries." This statement was based on a

sentence from sentence from page 26, lines 12-15 of Jindal *et al.*, which was cited by the Examiner without the bolded part:

"The integrated coupling of various dimensions such as **micro column affinity chromatography with capillary reverse phase HPLC**/electrospray ionization mass spectrometry in an automated multi-dimensional system should permit a highly sensitive and highly selective approach to decoding complex mixtures."

To read this sentence as an explicit statement "that mass spectroscopy is the method of choice for studying libraries" is a clear misrepresentation. What the sentence says, when cited in full, is that coupling micro column affinity chromatography with capillary reverse phase HPLC/electrospray ionization mass spectrometry "should" permit a highly sensitive and selected approach to decoding complex mixtures. There is nothing in the statement that would indicate that electrospray ionization mass spectrometry alone, without being combined with micro column affinity chromatography would provide the stated benefits. Indeed, the entire disclosure of Jindal *et al.*, including Figures 1 and 2, clearly shows that Jindal *et al.* always use mass spectrometry as part of a complex analytical system, following a variety of chromatographic separation steps. Furthermore, there is nothing in this statement that could be reasonably read to mean that "*mass spectrometry is the method of choice for studying libraries*" as the Examiner states, although mass spectrometry methods are described as methods of detection elsewhere (*e.g.* page 4, lines 9-22).

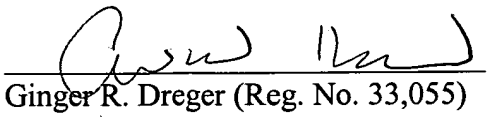
CONCLUSION

For the reasons given above, and for the reasons set forth in the Appeal Brief filed on December 2, 2005, Appellants maintain that the invention claimed in claims 58, 59, 61, 65, 81-89, 93, 85 and 96 of the present application is unobvious over the cited combinations of references, and thus the outstanding rejections should be reversed.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (referencing Attorney's Docket No. 39750-0002DV1).

Respectfully submitted,

Date: June 21, 2006



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